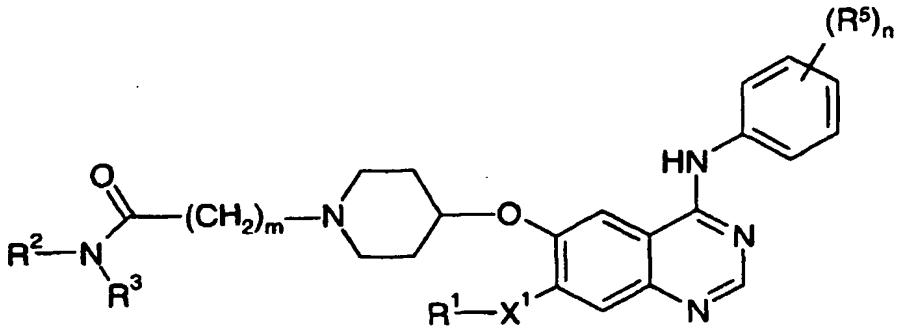
CLAIMS

1. A quinazoline derivative of the Formula I:



I

wherein **n** is 0, 1, 2 or 3,

each R^5 is independently selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, sulfamoyl, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylsulfamoyl, and N,N-di-[(1-6C)alkyl]sulfamoyl, $C(O)NR^6R^7$ where R^6 and R^7 are independently selected from hydrogen, optionally substituted (1-6C)alkyl, optionally substituted (3-8C)cycloalkyl or optionally substituted aryl, or R^6 and R^7 together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring which may contain additional heteroatoms;

X^1 is a direct bond or O;

R^1 is selected from hydrogen and (1-6C)alkyl, wherein the (1-6C)alkyl group is optionally substituted by one or more substituents, which may be the same or different, selected from hydroxy and halogeno, and/or a substituent selected from amino, nitro, carboxy, cyano, halogeno, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl, sulfamoyl, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino;

m is 0, 1, 2 or 3;

R^2 is hydrogen or (1-6C)alkyl; and

R^3 is (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl or (1-6C)alkoxy, any of which can be optionally substituted on a carbon atom by a (1-6C)alkoxy, amino, (1-6C)alkylamino, di-(1-6C)alkylamino, or a group $S(O)_s$(1-6C)alkyl where s is 0, 1 or 2, or a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms selected from oxygen, sulfur or NR^8 where R^8 is hydrogen, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylsulfonyl or (1-6C)alkylcarbonyl;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated 5 or 6 membered heterocyclic ring which optionally contains additional heteroatoms selected from oxygen, S, SO or $S(O)_2$ or NR^8 where R^8 is as defined above;

provided that the quinazoline derivative is not:

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonyl]-piperidin-4-yl-oxy}-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(diethylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(pyrrolidin-1-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(4-methyl-piperazin-1-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-ethoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-(2-methoxy-ethoxy)-quinazoline;

4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(ethylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(isopropylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonylmethyl]-piperidin-4-yl-oxy}-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylmethyl]-piperidin-4-yl-oxy}-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(methylamino)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(dimethylamino)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(pyrrolidin-1-yl)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylmethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(methylamino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(2-methoxyethyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(3-methoxypropyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(N-methyl-N-3-methoxypropyl)amino)carbonyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylethyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline; or

4-[(3-chloro-4-fluorophenyl)amino]-6-{1-[(morpholin-4-yl)carbonylpropyl]-piperidin-4-yl-oxy}-7-methoxy-quinazoline;
or a pharmaceutically acceptable salt thereof.

2. A quinazoline derivative according to claim 1, wherein n is 1, 2 or 3.

3. A quinazoline derivative according to claim 1 or claim 2, wherein n is 2 or 3.

4. A quinazoline derivative according to any one of claims 1 to 3, wherein n is 2.

5. A quinazoline derivative according to any one of claims 1 to 3, wherein n is 3.

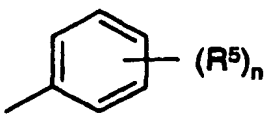
6. A quinazoline derivative according to any one of the preceding claims, wherein each group R^5 is a halogeno group.

7. A quinazoline derivative according to any one of the preceding claims, wherein each group R^5 is selected from chloro and fluoro.

8. A quinazoline derivative according to any one of the preceding claims, which includes a group R^5 positioned at an ortho- (2-) position on the benzene ring to which it is attached.

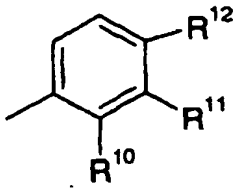
9. A quinazoline derivative according to claim 8, wherein the group R^5 positioned at the ortho- (2-) position is fluoro.

10. A quinazoline derivative according to any one of the preceding claims, wherein in the Formula I, the group of sub-formula (i):



(i)

is a group of sub-formula (ii):



(ii)

wherein (a) one of R^{10} or R^{12} is hydrogen and the other is halogeno, and R^{11} is halogeno, or (b) R^{10} is halogeno, R^{11} is halogeno and R^{12} is selected from hydrogen or halogeno, or (c) R^{10} is fluoro, R^{11} is chloro, and R^{12} is selected hydrogen or fluoro.

11. A quinazoline derivative according to claim 10, wherein one of R^{10} or R^{12} is hydrogen and the other is fluoro, and R^{11} is chloro.

12. A quinazoline derivative according to claim 10, wherein R^{10} is fluoro, R^{11} is chloro, and R^{12} is hydrogen.

13. A quinazoline derivative according to claim 10, wherein R^{10} is fluoro, R^{11} is chloro, and R^{12} is fluoro.

14. A quinazoline derivative according to any one of the preceding claims, wherein X^1 is oxygen.

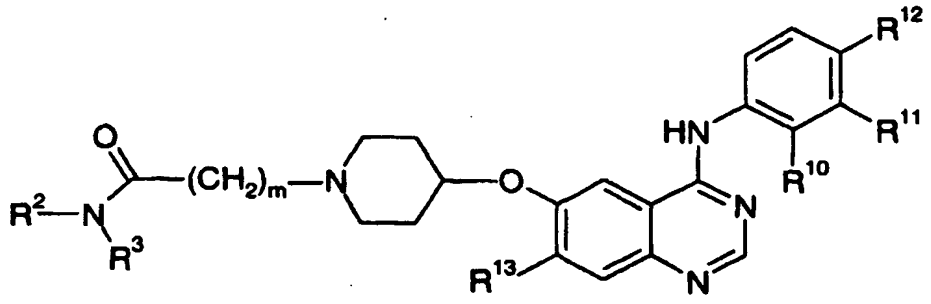
15. A quinazoline derivative according to any one of the preceding claims, wherein R^1 is selected from hydrogen, (1-6C)alkyl and (1-6C)alkoxy(1-6C)alkyl, wherein any (1-6C)alkyl group in R^1 optionally bears one or more hydroxy or halogeno substituents

16. A quinazoline derivative according to claim 15, wherein R^1 is selected from (1-6C)alkyl, which optionally bears one or more hydroxy or halogeno substituents.

17. A quinazoline derivative according to any one of the claims 1 to 13, wherein R^1-X^1- is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

18. A quinazoline derivative according to claim 17, wherein R^1-X^1- is methoxy.

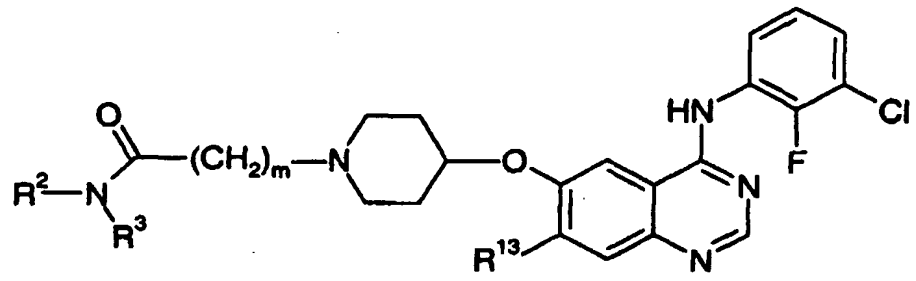
19. A quinazoline derivative according to claim 1 of Formula IA:



IA

wherein R^2, R^3 and m are as defined in claim 1, R^{10}, R^{11} and R^{12} are as defined in any one of claims 10 to 13 , and R^{13} is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

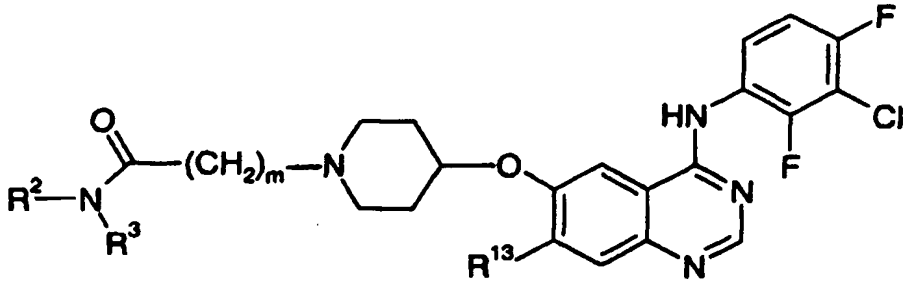
20. A quinazoline derivative according to claim 1 of Formula IB:



IB

wherein R^2, R^3 and m are as defined in claim 1 and R^{13} is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

21. A quinazoline derivative according to claim 1 of Formula IC:



IC

wherein R^2, R^3 and m are as defined in claim 1 and R^{13} is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy.

22. A quinazoline derivative according to any one of claims 19 to 21, wherein R^{13} is methoxy.

23. A quinazoline derivative according to any one of the preceding claims, wherein m is 0 or 1.

24. A quinazoline derivative according to any one of the preceding claims, wherein m is 1.

25. A quinazoline derivative according to any one of the preceding claims, wherein R^2 is hydrogen or (1-3C)alkyl.

26. A quinazoline derivative according to any one of the preceding claims, wherein R^2 is hydrogen or methyl.

27. A quinazoline derivative according to any one of the preceding claims, wherein R^2 is hydrogen.

28. A quinazoline derivative according to any one of the preceding claims, wherein R^3 is (1-6C)alkyl.

29. A quinazoline derivative according to any one of the preceding claims, wherein R^3 is (1-3C)alkyl.

30. A quinazoline derivative according to any one of the preceding claims, wherein R^3 is methyl.

31. A quinazoline derivative according to claim 1, which is selected from one or more of the following:
4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]-oxy}quinazoline;

4-(3-chloro-2-fluoroanilino)-6-{[1-(N,N-dimethylcarbamoylmethyl)piperidin-4-yl] oxy}-7-methoxyquinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(morpholin-4-ylcarbonylmethyl)piperidin-4-yl]oxy}- quinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(pyrrolidin-1-ylcarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoyl)piperidin-4-yl]oxy} quinazoline;

4-(3-chloro-2-fluoroanilino)-6-{[1-(N-(2-dimethylaminoethyl)carbamoyl)piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-chloro-2-fluoroanilino)-6-{[1-(N,N-dimethylcarbamoyl)piperidin-4-yl]oxy}7-methoxy-quinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]oxy} quinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-[2-pyrrolidin-1-ylethyl]carbamoyl) piperidin-4-yl]oxy}quinazoline;

4-(3-chloro-2,4-difluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline;

4-(3-chloro-2-fluoroanilino)-6-{[1-(N-ethylcarbamoylmethyl)piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-[2-(pyrrolidin-1-yl)ethyl]carbamoylmethyl)piperidin-4-yl]oxy}quinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-(2-methoxyethyl)carbamoylmethyl)piperidin-4-yl]oxy}quinazoline;

4-(3-chloro-2-fluoroanilino)-6-{[1-(N-(2-dimethylaminoethyl)carbamoylmethyl)piperidin-4-yl]oxy}-7-methoxyquinazoline;

4-(3-chloro-2-fluoroanilino)-7-methoxy-6-({1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]piperidin-4-yl}oxy)quinazoline;

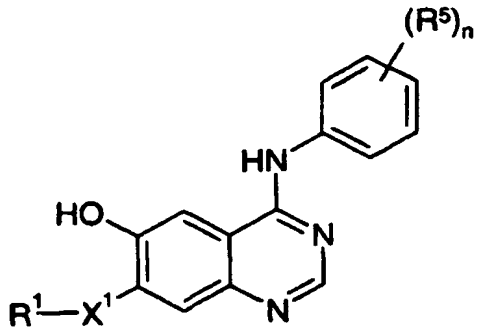
4-(3-chloro-2-fluoroanilino)-7-methoxy-6-({1-[2-(piperazin-1-yl)-2-oxoethyl]piperidin-4-yl}oxy)quinazoline; and

4-(3-chloro-2,4-difluoroanilino)-7-methoxy-6-({1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]piperidin-4-yl}oxy)quinazoline;

or a pharmaceutically acceptable salt thereof.

32. A process for preparing a quinazoline derivative according to any one of the preceding claims, which comprises either

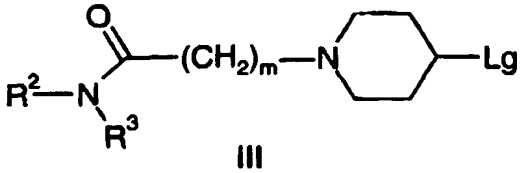
Process (a) reacting a compound of the Formula II:



II

wherein R^1, X^1, R^5 and n have any of the meanings defined in claim 1 except that any functional group is protected if necessary,

with a compound of the Formula III:

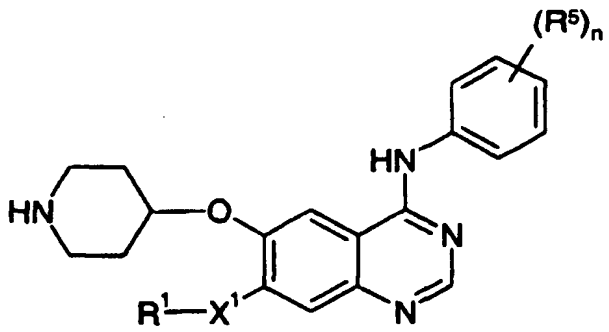


III

wherein R^2, R^3 and m have any of the meanings defined in claim 1 except that any functional group is protected if necessary and Lg is a displaceable group, wherein the reaction is conveniently performed in the presence of a suitable base,

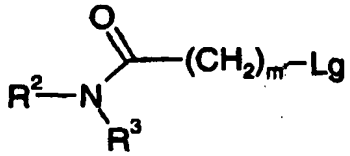
Process (b) modifying a substituent in or introducing a substituent into another quinazoline derivative of Formula I or a pharmaceutically acceptable salt thereof, as hereinbefore defined except that any functional group is protected if necessary;

Process (c) reacting a compound of Formula IV:

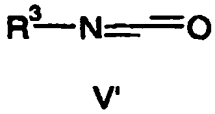


IV

where R^1, X^1, R^5 and n are as defined in relation to Formula I except that any functional group is protected if necessary, with a compound of the Formula V or V':



V



V'

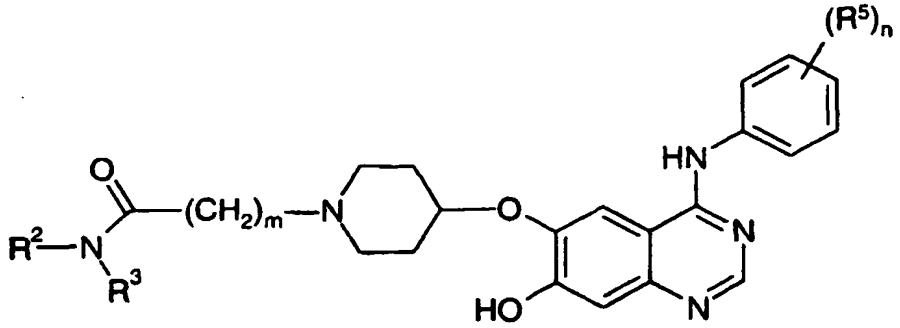
wherein R^2 and R^3 are as defined above and m' is 0, 1, 2 or 3, provided that it is not 0 when R^2 is hydrogen, and Lg is a displaceable group;

Process (d) removal of a protecting group from a quinazoline derivative of Formula I, or a pharmaceutically acceptable salt thereof;

Process (e) reacting a compound of the Formula II as hereinbefore defined with a compound of the Formula III as defined hereinbefore except Lg is OH under Mitsunobu conditions;

Process (f) for the preparation of those compounds of the Formula I wherein R^1-X^1 is a hydroxy group, cleavage of a quinazoline derivative of the Formula I wherein R^1-X^1 is a (1-6C)alkoxy group;

Process (g) for the preparation of those compounds of the Formula I wherein X^1 is O and R^1 is not hydrogen, by the reaction of a compound of the Formula VI:

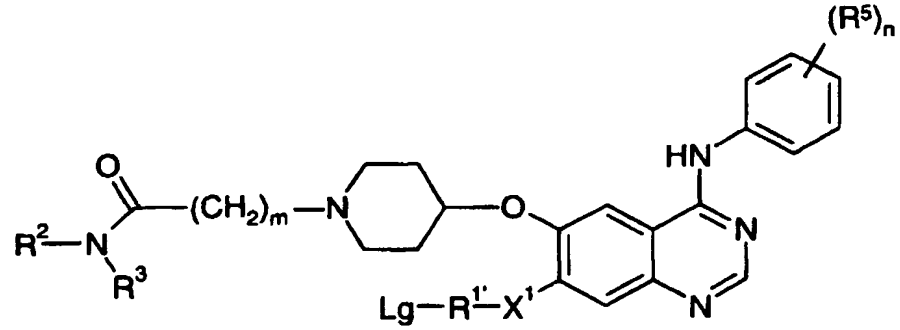


VI

wherein R^2, R^3, R^5, m and n have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a compound of the formula R^1-Lg, wherein R^1 has any of the meanings defined in claim 1 except that it is not hydrogen and except that any functional group is protected if necessary and Lg is a displaceable group;

Process (h) for the preparation of those compounds of the Formula I wherein R^1 contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, alkylation of a quinazoline derivative of the Formula I wherein or R^1 contains a hydroxy group or a primary or secondary amino group as appropriate;

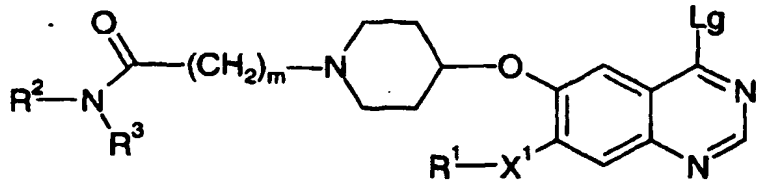
Process (i) for the preparation of those compounds of the Formula I wherein R^1 is substituted by a group T, wherein T is selected from (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino, (1-6C)alkylthio, (1-6C)alkylsulfinyl and (1-6C)alkylsulfonyl, the reaction of a compound of the Formula VII:



VII

wherein R^2, R^3, R^5, X^1, n and m have any of the meanings defined hereinbefore except that any functional group is protected if necessary, $R^{1'}$ is a group R^1 as defined herein except that any T groups are replaced with Lg, and Lg is a displaceable group (for example chloro or bromo) with a compound of the formula TH, wherein T is as defined above except that any functional group is protected if necessary;

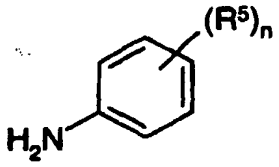
Process (j) reacting a compound of the Formula VIII:



VIII

wherein R^1, R^2, R^3, X^1, and m have any of the meanings defined in claim 1 except that any functional group is protected if necessary and Lg is a displaceable group as hereinbefore defined,

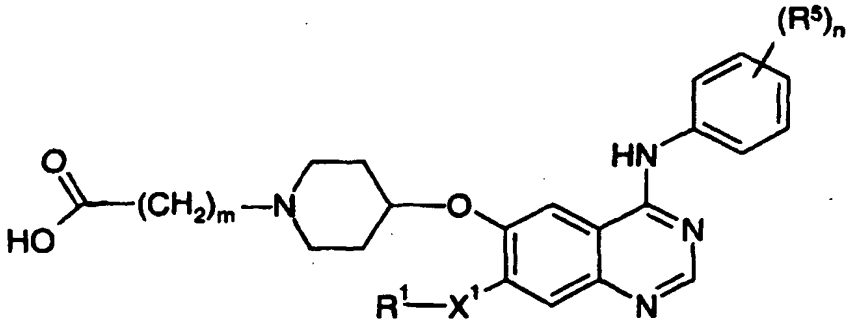
with an aniline of the Formula IX:



IX

wherein R^5 and n have any of the meanings defined in claim 1 except that any functional group is protected if necessary, and wherein the reaction is conveniently performed in the presence of a suitable acid;

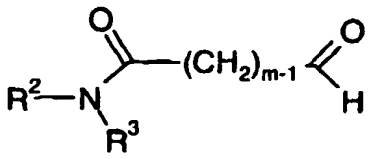
Process (k) for the preparation of those compounds of the Formula I wherein m is 1, 2 or 3, coupling of a compound of Formula X:



X

wherein m is 1, 2 or 3 and R^1, X^1, R^5, and n are as hereinbefore defined in claim 1, except any functional group is protected if necessary, with a primary or secondary amine of formula R^2NHR^3 where R^2 and R^3 are as defined in claim 1;

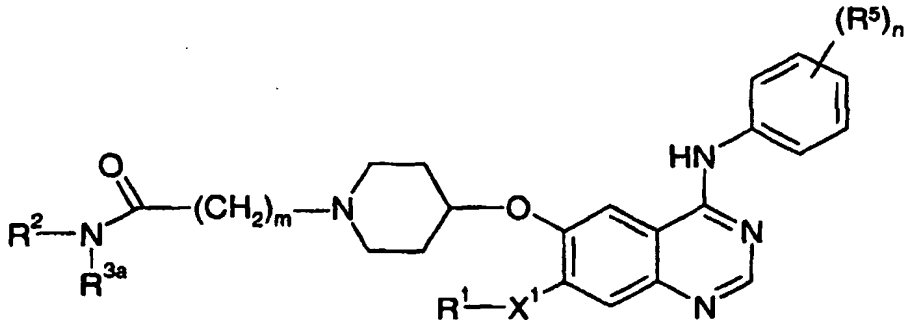
Process (l) By reacting a compound of Formula IV as defined above except that any functional group is protected if necessary, with a compound of the Formula V'':



V''

using a reductive amination procedure,

Process (m) for the preparation of those compounds of the Formula I wherein R^3 is (2-6C)alkyl substituted on a carbon atom by an amino, (1-6C)alkylamino, di-(1-6C)alkylamino or a saturated 5 or 6 membered heterocyclic ring which contains NR^8 where R^8 is as defined in claim 1, by reacting a compound of the Formula XX:



XX

wherein R^{3a} is Lg-(2-6C)alkyl, wherein Lg is a displaceable group and wherein R^1, R^2, X^1, R^5, m and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary,

with ammonia or with a suitable primary or secondary amine,

and whereafter any of said processes, any protecting group that is present is removed.

33. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in any one of claims 1 to 31 in association with a pharmaceutically-acceptable diluent or carrier.

34. A quinazoline derivative of the Formula I as defined in any one of claims 1 to 31, or a pharmaceutically acceptable salt thereof, for use as a medicament.

35. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in any one of claims 1 to 31 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal.

36. A method for producing an anti-proliferative effect in a warm-blooded animal in need of such treatment which comprises administering to said animal a quinazoline derivative of the Formula I, or a pharmaceutically acceptable salt thereof, as defined any one of claims 1 to 31.

37. A compound of the Formula VI, VII, VIII, X or XX as defined in claim 32 or a salt thereof.